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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/931,704	08/16/2001	Giorgio Senaldi	A-695	3429

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U.S. Patent Operations/KLN
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EXAMINER
HUYNH, PHUONG N

ART UNIT	PAPER NUMBER
1644	8

DATE MAILED: 02/10/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/931,704	Applicant(s) SENALDI, GIORGIO
	Examiner " Neon" Phuong Huynh	Art Unit 1644

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 November 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *38-63* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *38-63* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *11/20/02* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. Claims 38-63 are pending.

2. The following new grounds of objection and rejection are necessitated by the amendment filed 11/20/02.

3. Claims 47-49 are objected to because the term "is comprises" should have been "comprises".

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 38-63 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for (1) a method for increasing antigen-specific IgE-production comprising administering to a patient a therapeutically effective amount of a polypeptide comprising SEQ ID NO: 2 or 5 or a polypeptide encoded by a nucleic acid sequence of SEQ ID NO: 1, 3 or 4 and (2) a method for detection using antibody such as monoclonal antibody, humanized antibody, fully human antibody, polyclonal antibody, chimeric antibody, CDR-grafted antibody, bispecific, single chain or fragment thereof which specifically binds a polypeptide selected from the group consisting of a) a polypeptide comprising the amino acid sequence of SEQ ID NO: 2 or 5 or b) a polypeptide encoded by a nucleic acid sequence of SEQ ID NO: 1, 3 or 4; (3) the said method wherein the antibody comprises a variable region, an Fab, Fab' fragment, or Fc fragment, (4) the said method wherein said antibody is bound to a detectable label, (5) the said method wherein the antibody is produced from a hybridoma, **does not** reasonably provide enablement for (1) a method for the treatment of *any* IgE-related disease comprising administering to a patient a therapeutically effective amount of *any* isolated and purified antibody or fragment thereof such as monoclonal antibody, humanized antibody, fully human antibody, any antibody further comprises human chemical modification, polyclonal antibody, chimeric antibody, CDR-grafted antibody, bispecific, single chain, hetero-antibody or fragment thereof which specifically binds to *any* polypeptide such as the ones specified in claim 38, (2) the said method wherein said antibody comprises a variable region fragment, an Fab, fragment, or an Fc fragment, (3) the said method

wherein said antibody is bound to a detectable label, (4) the said method wherein the antibody is produced from a hybridoma, (4) a method for the treatment of *any* IgE-related disease such as Type I allergic disease, allergic rhinitis, eczema, dermatitis, pollinosis, or asthma comprising administering to a patient a therapeutically effective amount of *any* isolated and purified antibody or fragment thereof such as monoclonal antibody, humanized antibody, fully human antibody, any antibody further comprises human chemical modification, polyclonal antibody, chimeric antibody, CDR-grafted antibody, bispecific, single chain, hetero-antibody or fragment thereof which specifically binds to *any* polypeptide such as the ones specified in claim 38, (5) a method for "modulating IgE levels" in any patient comprising administering to said patient a therapeutically effective amount of any isolated or purified antibody or fragment thereof which specifically binds to any polypeptide such as the ones recited in claim 58, (6) the method for "modulating IgE levels" in any patient wherein the IgE levels in a patient are decreased or increased, (7) a method of "modulating IgE levels" in any patient comprising administering to said patient a therapeutically effective amount of any polypeptide such as the ones recited in claim 61, (8) the method of "modulating IgE levels" in any patient comprising administering to said patient a therapeutically effective amount of any polypeptide such as the ones recited in claim 61 wherein the IgE levels in a patient are "decreased", (9) the method of "modulating IgE levels" in any patient comprising administering to said patient a therapeutically effective amount of any polypeptide that is at least "70% identical" to the polypeptide comprising the amino acid sequence of SEQ ID NOS: 2 or 5, any polypeptide that is at least "70% identical" to the polypeptide encoded by a nucleic acid sequence of SEQ IDNO: 1, 3 or 4, any "biologically active fragment" of any polypeptide mentioned above, or any "derivative or variant" of any polypeptide mentioned above for treating any IgE related disease or modulating IgE levels. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient

to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The specification discloses only NNT-1 treatment increases antigen specific IgE in mice either induced with anti-KLH or in NNT-1 transgenic mice (See pages 37-38 of the specification) and detection of anti-KLH IgE in *in vitro* (page 39). The specification discloses only a human NNT-1 polypeptide comprising the amino acid sequence of SEQ ID NO: 2 and a mouse NNT-1 polypeptide comprising the amino acid sequence of SEQ ID NO: 5 which encoded by the polynucleotides of SEQ ID NO: 1 and 3, respectively. The specification on pages 17-18 defines the term NNT-1 inhibitor is any agent which is capable of inhibiting the production, activity, or expression of NNT-1 polypeptide and/or its receptor, including but not limited to ribozymes, and small molecules. The term "selective binding agents" refers to any molecule which a capable of specifically binding to an NNT-1 polypeptide, fragment, derivative or variant thereof or the NNT-1 receptor such as antibodies, derivative thereof, polypeptides, fusion polypeptides, part peptide, part antibody, soluble receptor proteins, small molecules, anti-sense oligonucleotides and other molecules having binding specificity. The specification defines the term "biological active fragment" on page 11 is any fragment from 1-20 amino acids from either the C-terminus or the N-terminus or both termini of the NNT-1 polypeptide that has qualitatively a substantially similar type of biological activity such as the ability to act as a growth factor for neurons and increases T and B cell production as the full length mature NNT-1 polypeptide where the activity is at least 50% of the activity of the full length polypeptide. The specification on page 12 defines the term "variant" as any NNT-1 polypeptide having one or more amino acid substitutions, deletions, and additions, any NNT-1 variants may have from 1 to 100 or more than 100 amino acid substitutions, insertions, additions and/or deletion.

The specification does not teach any methods mentioned above using any antibody or fragment thereof that binds specifically to any polypeptide that is at least "70% identical" to the polypeptide comprising the amino acid sequence of SEQ ID NO: 2 or 5, or any polypeptide encoded by a nucleic acid sequence of SEQ ID NOS: 1, 3 or 4, much less of "biological fragment" and "derivative or variant" of any polypeptide mentioned above because of the following reasons. Sequence identity does not equate with function with the polypeptide. Ngo *et al,* of record, teach that the amino acid positions within the polypeptide/protein that can tolerate change such as conservative substitution or no substitution, addition or deletion which are critical to maintain the protein's structure/function will require guidance (See Ngo et al., 1994, The

Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495). There is insufficient guidance and working examples as to which amino acid residue within the NNT-1 polypeptide of SEQ IN NO: 2 or 5 and fragment thereof mentioned above can be added, deleted, substitute and chemically modified and whether the resulting polypeptide and fragment thereof would maintain both the structure and function as NNT-1 of SEQ ID NO: 2 and 5, in turn, for a method of treating any IgE related diseases mentioned above, or modulating IgE levels in a patient. Further, the specification fails to provide guidance (the specific amino acid sequence, binding specificity, the epitope to which the antibody binds such as how to make such antibody with antagonistic activity (decreases IgE) or agonistic activity (increases IgE) for a method of modulating and treating any disease such as type I allergic disease mentioned above.

Abaza *et al* teach that even a single amino acid substitution outside the antigenic site can exert drastic effects on the reactivity of a protein with monoclonal antibody against the site (See abstract, in particular).

Kuby *et al* teach that antibody epitopes (B cell epitopes) are not linear and are comprised of complex three-dimensional array of scattered residues which will fold into specific conformation that contribute to binding (See Kuby 1994, page 94, in particular). Immunization with a peptide fragment derived from a full-length polypeptide may result in **antibody specificity** that differs from the antibody specificity directed against the native full-length polypeptide. Given the indefinite number of undisclosed "biological active fragment thereof", "derivative or variant" and polypeptide having 30% difference in sequence identity, it is unpredictable which undisclosed antibody mentioned above would bind specifically to a polypeptide of SEQ ID NO: 2 or 5, or the polypeptide encoded by the polynucleotide of SEQ ID NO: 1, 3 or 4. Given the lack of guidance as the specificity of the claimed antibody and the epitope to which the antibody binds (antigenic determinant) that would increase or decrease IgE level in vivo, it is unpredictable which undisclosed antibody is effective for treating any IgE-related disease, especially allergic disease since it is associated with an increase in IgE levels. In the absence of guidance as to which epitope (amino acid residues) to which the antibody binds, it is also unpredictable which antibody in the claimed method of modulating the levels of IgE because "modulating" can increase or decrease the levels of IgE. Further, there are no in vivo working examples demonstrating any antibody such as monoclonal antibody, humanized antibody, fully human antibody, any antibody further comprises human chemical modification, polyclonal antibody, chimeric antibody, CDR-grafted antibody, bispecific, single chain, hetero-antibody or fragment

thereof mentioned above would even bind specifically to the NNT-1 polypeptides of SEQ ID NO: 2 or 5, let alone using it to treat any IgE related disease, to suppress, to inhibit or modulate (increase or decrease) the levels of IgE in a patient.

The '370 patent, of record, teaches that the inherent problem with chimeric antibody has been a loss of affinity for the antigen, which means more antibody will have to be injected into a patient at higher cost and greater risk of adverse effects such as serum sickness (See column 2 lines 12-27, in particular). In the absence of in vivo working examples, it is unpredictable for the following reasons: (1) the antibody may be inactivated before producing an effect, i.e. such as inherently short half-life of the antibody; (2) the antibody may not reach the target area; and (3) other functional properties, known or unknown, may make the antibody unsuitable for *in vivo* therapeutic use, i.e. such as serum sickness which prohibitive to the use of antibody for such treatment.

With regard to a method of modulating IgE levels by administering a polypeptide as recited in claims 61-63, there is insufficient guidance as to any polypeptide that is at least "70% identical" to any polypeptide mentioned above because Attwood *et al* teach that protein function is context-dependent and the state of the art of making functional assignments merely on the basis of some degree of similarity between sequences and the current structure prediction methods is unreliable (See figure, entire document). Skolnick *et al.* teach that squence-based methods for function prediction are inadequate and knowing a protein's structure does not necessary tell one it's function (See entire document, Abstract in particular). It is known in the art that even single amino acid changes or differences in a protein's amino acid sequence can have dramatic effects on the protein's function. For example, Mikayama *et al.*, teach that the human glycosylation-inhibiting factor (GIF) protein differs from human macrophage migration inhibitory factor (MIF) by a single amino acid residue (Figure 1 in particular). Yet, Mikayama *et al.* teach further that GIF is unable to carry out the function of MIF and MIF does not demonstrate GIF bioactivity (Abstract in particular). Thus, knowing the sequence alone will not inherently tell us the function. Given the indefinite number of undisclosed polypeptide that has 68 amino acids difference in SEQ ID NO: 2 or SEQ ID NO: 5 (30% difference), it is unpredictable which undisclosed polypeptide would increase or decrease IgE levels, in turn, would be useful for treating any IgE related diseases. Further, there is insufficient guidance as to which amino acid within the full length polypeptide of SEQ ID NO: 2 or 5 could tolerate change such as addition, deletion or amino acid substitution and whether the resulting polypeptide such as variant and derivative

thereof would have the same structure, much less having the same function, in turn, would be useful for modulating IgE levels such as decreasing IgE levels in vivo for treating IgE related diseases. In contrast, the specification discloses only that treating NNT-1 transgenic mice with the full-length polypeptide of SEQ ID NO: 2 or 5 increases IgE levels in serum (page 38, Example II, in particular). The specification does not teach administering any polypeptide would "decrease" IgE levels. Given the indefinite number of undisclosed "biological fragment", "derivative or variant" of any "polypeptide having only 70% identity" to any polypeptide mentioned above, it is unpredictable which undisclosed "biological fragment", "derivative or variant" would be useful for modulating IgE levels such as decreasing or increasing said IgE levels. Further there is insufficient working example demonstrating that any undisclosed "biological fragment" or "derivative or variant" mentioned above is effective for modulating IgE levels, whether it is increasing or decreasing IgE levels for treating any IgE related diseases.

For these reasons, it would require undue experimentation of one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

Applicants' arguments filed 11/20/02 have been fully considered but are not found persuasive.

Applicants' position is that (1) claims 1-37 have been canceled and (2) the newly added claims 38-63 are directed to methods of treating IgE related disease or modulating IgE levels in a patient by administration of a defined class of molecules.

However, the specification does not teach any methods mentioned above using any antibody or fragment thereof that binds specifically to any polypeptide much less any "biological fragment" and "derivative or variant" thereof because sequence identity does not equate with function. There is insufficient guidance and working examples as to which amino acid residue within the NNT-1 polypeptide of SEQ IN NO: 2 or 5 and fragment thereof mentioned above can be added, deleted, substitute and chemically modified and whether the resulting polypeptide and

fragment thereof would maintain the structure and function as NNT-1 polypeptide of SEQ ID NO: 2 and 5, in turn, for a method of treating any IgE related diseases to modulate IgE levels in a patient. Further, the specification fails to provide guidance with respect to (1) which amino acid within the full-length polypeptide of SEQ ID NO: 2 or 5 can be modified and whether the resulting polypeptide has biological function as the full-length polypeptide of SEQ ID NO: 2 or 5, (2) the binding specificity of the claimed antibodies, particularly the epitope to which the antibodies bind that can either increase or decrease IgE levels in vivo for a method of modulating IgE level or treating any disease such as type I allergic disease mentioned above. Abaza *et al* teach that even a single amino acid substitution outside the antigenic site can exert drastic effects on the reactivity of a protein with monoclonal antibody against the site (See abstract, in particular).

Kuby *et al* teach that antibody epitopes (B cell epitopes) are not linear and are comprised of complex three-dimensional array of scattered residues which will fold into specific conformation that contribute to binding (See Kuby 1994, page 94, in particular). Immunization with a peptide fragment derived from a full-length polypeptide may result in **antibody specificity** that differs from the antibody specificity directed against the native full-length polypeptide. Given the indefinite number of undisclosed "biological active fragment thereof", "derivative or variant" and polypeptide having 30% difference in sequence identity, it is unpredictable which undisclosed antibody mentioned above would bind specifically to a polypeptide of SEQ ID NO: 2 or 5, or a polypeptide encoded by polynucleotide of SEQ ID NO: 1, 3 or 4. Given the lack of guidance as the specificity of the claimed antibody and the epitope to which the antibody binds that would increase or decrease IgE level, it is unpredictable whether the claimed antibody is useful for treating any IgE-related disease, especially allergic disease since it is associated with an increase in IgE levels. In the absence of guidance as to which epitope to which the antibody binds, it is also unpredictable which antibody in the claimed method can modulates the levels of IgE because the term "modulating" can increase or decrease the levels of IgE, which is mutually exclusive. Further, there are no in vivo working examples demonstrating any antibody such as monoclonal antibody, humanized antibody, fully human antibody, any antibody further comprises human chemical modification, polyclonal antibody, chimeric antibody, CDR-grafted antibody, bispecific, single chain, hetero-antibody or fragment thereof mentioned above would bind specifically to the NNT-1 polypeptides of SEQ ID NO: 2 or 5, much less effective for treating any IgE related disease.

With regard to a method of modulating IgE levels by administering a polypeptide as recited in claims 61-63, there is insufficient guidance as to any polypeptide that is at least "70% identical" to any polypeptide mentioned above because Attwood *et al* teach that protein function is context-dependent and the state of the art of making functional assignments merely on the basis of some degree of similarity between sequences and the current structure prediction methods is unreliable (See figure, entire document). Skolnick *et al.* teach that squence-based methods for function prediction are inadequate and knowing a protein's structure does not necessary tell one it's function (See entire document, Abstract in particular). It is known in the art that even single amino acid changes or differences in a protein's amino acid sequence can have dramatic effects on the protein's function. For example, Mikayama *et al.*, teach that the human glycosylation-inhibiting factor (GIF) protein differs from human macrophage migration inhibitory factor (MIF) by a single amino acid residue (Figure 1 in particular). Yet, Mikayama *et al.* teach further that GIF is unable to carry out the function of MIF and MIF does not demonstrate GIF bioactivity (Abstract in particular). Thus, knowing the sequence alone will not inherently tell us the function. Given the indefinite number of undisclosed polypeptide that has 68 amino acids difference in SEQ ID NO: 2 or SEQ ID NO: 5 (30% difference), it is unpredictable which undisclosed polypeptide would increase or decrease IgE levels, in turn, would be useful for treating any IgE related diseases. Further, there is insufficient guidance as to which amino acid within the full length polypeptide of SEQ ID NO: 2 or 5 could tolerate change such as addition, deletion or amino acid substitution and whether the resulting polypeptide such as variant and derivative thereof would have the same structure, much less having the same function, in turn, would be useful for modulating IgE levels such as decreasing IgE levels in vivo for treating IgE related diseases. In contrast, the specification discloses only that treating NNT-1 transgenic mice with the full-length polypeptide of SEQ ID NO: 2 or 5 <u>increases</u> IgE levels in serum (page 38, Example II, in particular). The specification does not teach administering any polypeptide would "decrease" IgE levels.

6. Claims 38-63 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** of (1) a method for the treatment of *any* IgE-related disease comprising administering to a patient a therapeutically effective amount of *any* isolated and purified antibody or fragment thereof such as monoclonal antibody, humanized antibody, fully human antibody, any antibody further comprises human chemical modification, polyclonal antibody, chimeric antibody, CDR-grafted antibody, bispecific, single chain, hetero-antibody or fragment thereof which specifically binds to *any* polypeptide such as the ones specified in claim 38, (2) the said method wherein said antibody comprises a variable region fragment, an Fab, fragment, or an Fc fragment, (3) the said method wherein said antibody is bound to a detectable label, (4) the said method wherein the antibody is produced from a hybridoma, (4) a method for the treatment of *any* IgE-related disease such as Type I allergic disease, allergic rhinitis, eczema, dermatitis, pollinosis, or asthma comprising administering to a patient a therapeutically effective amount of *any* isolated and purified antibody or fragment thereof such as monoclonal antibody, humanized antibody, fully human antibody, any antibody further comprises human chemical modification, polyclonal antibody, chimeric antibody, CDR-grafted antibody, bispecific, single chain, hetero-antibody or fragment thereof which specifically binds to *any* polypeptide such as the ones specified in claim 38, (5) a method for "modulating IgE levels" in any patient comprising administering to said patient a therapeutically effective amount of any isolated or purified antibody or fragment thereof which specifically binds to any polypeptide such as the ones recited in claim 58, (6) the method for "modulating IgE levels" in any patient wherein the IgE levels in a patient are decreased or increased, (7) a method of "modulating IgE levels" in any patient comprising administering to said patient a therapeutically effective amount of any polypeptide such as the ones recited in claim 61, (8) the method of "modulating IgE levels" in any patient comprising administering to said patient a therapeutically effective amount of any polypeptide such as the ones recited in claim 61 wherein the IgE levels in a patient are "decreased", (9) the method of "modulating IgE levels" in any patient comprising administering to said patient a therapeutically effective amount of any polypeptide that is at least "70% identical" to the polypeptide comprising the amino acid sequence of SEQ ID NOS: 2 or 5, any polypeptide that is at least "70% identical" to the polypeptide encoded by a nucleic acid sequence of SEQ IDNO: 1, 3 or 4, any "biologically active fragment" of any polypeptide mentioned above, or any "derivative or variant" of any polypeptide mentioned above for treating any IgE related disease or modulating IgE levels.

The specification discloses only NNT-1 treatment increases antigen specific IgE in mice induced with anti-KLH and in NNT-1 transgenic mice (See pages 37-38 of the specification) and detection of anti-KLH IgE in *in vitro* (page 39). The specification discloses only a human NNT-1 polypeptide comprising the amino acid sequence of SEQ ID NO: 2 and a mouse NNT-1 polypeptide comprising the amino acid sequence of SEQ ID NO: 5 which encode by the polynucleotides of SEQ ID NO: 1 and 3, respectively. The specification on pages 17-18 defines the term NNT-1 inhibitor is any agent which is capable of inhibiting the production, activity, or expression of NNT-1 polypeptide and/or its receptor, including but not limited to ribozymes, and small molecules. The term "selective binding agents" refers to any molecule which a capable of specifically binding to an NNT-1 polypeptide, fragment, derivative or variant thereof or the NNT-1 receptor such as antibodies, derivative thereof, polypeptides, fusion polypeptides, part peptide, part antibody, soluble receptor proteins, small molecules, anti-sense oligonucleotides and other molecules having binding specificity. The specification defines the term "biological active fragment" on page 11 is any fragment from 1-20 amino acids from either the C-terminus or the N-terminus or both termini of the NNT-1 polypeptide that has qualitatively a substantially similar type of biological activity such as the ability to act as a growth factor for neurons and increases T and B cell production as the full length mature NNT-1 polypeptide where the activity is at least 50% of the activity of the full length polypeptide. The specification on page 12 defines the term "variant" as any NNT-1 polypeptide having one or more amino acid substitutions, deletions, and additions, any NNT-1 variants may have from 1 to 100 or more than 100 amino acid substitutions, insertions, additions and/or deletion.

With the exception of the specific methods mentioned above, there is insufficient written description about the structure associated with function of any antibody that binds to (1) any polypeptide that is at least 70% identical to the polypeptide of comprising the amino acid sequence of SEQ ID NOS: 2 or 5, or the polypeptide encoded by a nucleic acid sequence of SEQ IDNO: 1, 3 or 4, (2) any "biologically active fragment" of any polypeptide comprising the amino acid sequence of SEQ ID NOS: 2 or 5, or any polypeptide encoded by a nucleic acid of SEQ ID NOS: 1, 3 or 4, any polypeptide that is at least "70% identical" to any polypeptide mentioned above; (3) any "derivative or variant" and (4) "biologically active fragment" thereof for a method of treating any IgE-related disease. Likewise, there is insufficient written description about a method for modulating the IgE levels wherein the IgE levels is increase or decrease by administering any polypeptide that is at least "70% identical" to the polypeptide of comprising

the amino acid sequence of SEQ ID NOS: 2 or 5, or any polypeptide that is at least "70% identical" to any polypeptide encoded by a nucleic acid sequence of SEQ IDNO: 1, 3 or 4 or any "biologically active fragment" and "derivative or variant" thereof for a method of modulating IgE levels, particularly where the IgE levels in a patient are "decreased". Note, the specification discloses only two polypeptide of SEQ ID NO: 2 and 5 from two species such as human and mouse and none of them have been demonstrated to "decrease" IgE levels as a method of modulating IgE. Finally, there is inadequate written description about the binding specificity and the epitope to which the antibody binds for a method for treating any IgE related disease such as the ones recited in claims 52-57, let alone the epitope to which the antibody binds that either "increase" or "decrease" IgE levels as a method for modulating IgE levels in a patient. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.* Applicant is directed to the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Applicants' arguments filed 11/20/02 have been fully considered but are not found persuasive.

Applicants' position is that (1) claims 1-37 have been canceled and (2) the newly added claims 38-63 are directed to methods of treating IgE related disease or modulating IgE levels in a patient by administration of a defined class of molecules.

However, there is insufficient written description about the structure associated with function of any antibody that binds to (1) any polypeptide that is at least 70% identical to the polypeptide of comprising the amino acid sequence of SEQ ID NOS: 2 or 5, or the polypeptide encoded by a nucleic acid sequence of SEQ IDNO: 1, 3 or 4, (2) any "biologically active fragment" of any polypeptide comprising the amino acid sequence of SEQ ID NOS: 2 or 5, or any polypeptide encoded by a nucleic acid of SEQ ID NOS: 1, 3 or 4, any polypeptide that is at least "70% identical" to any polypeptide mentioned above; (3) any "derivative or variant" and (4) "biologically active fragment" thereof for a method of treating any IgE-related disease. Likewise, there is insufficient written description about a method for modulating the IgE levels wherein the IgE levels is increase or decrease by administering any polypeptide that is at least "70% identical" to the polypeptide of comprising the amino acid sequence of SEQ ID NOS: 2 or 5, or any polypeptide that is at least "70% identical" to any polypeptide encoded by a nucleic acid sequence of SEQ IDNO: 1, 3 or 4 or any "biologically active fragment" and "derivative or

variant" thereof for a method of modulating IgE levels, particularly where the IgE levels in a patient are "decreased". Note, the specification discloses only two polypeptide of SEQ ID NO: 2 and 5 from two species such as human and mouse and none of them have been demonstrated to "decrease" IgE levels as a method of modulating IgE. Finally, there is inadequate written description about the binding specificity and the epitope to which the antibody binds for a method for treating any IgE related disease such as the ones recited in claims 52-57, let alone the epitope to which the antibody binds that either "increase" or "decrease" IgE levels as a method for modulating IgE levels in a patient.

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

8. Claims 42 and 48 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The recitation of "human chemical modifications" in claim 42 is indefinite and ambiguous. One of ordinary skill in the art cannot appraise the metes and bounds of the claimed invention.

The recitation of "Fab' of F(ab) fragment" in claim 48 is ambiguous and indefinite because Fab' is same as F(ab) fragment. Is it $F(ab)_2$? However, $F(ab)_2$ is not disclosed in the specification. As written, it is not clear which fragment of Fab Applicant intends to claim. One of ordinary skill in the art cannot appraise the metes and bounds of the claimed invention.

Applicants' arguments filed 11/20/02 have been fully considered but are not found persuasive.

Applicants' position is that (1) claims 1-37 have been canceled and (2) the newly added claims 38-63 are directed to methods of treating IgE related disease or modulating IgE levels in a patient by administration of a defined class of molecules.

However, Claim 42 still recites "human chemical modifications" and claim 48 still recites "Fab' of F(ab) fragment".

9. Claims 38-63 are free of prior art.

10. No claim is allowed.

11. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to "Neon" Phuong Huynh whose telephone number is (703) 308-4844. The examiner can normally be reached Monday through Friday from 9:00 am to 6:00 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

13. Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-7401.

Phuong N. Huynh, Ph.D.
Patent Examiner
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February 10, 2003

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